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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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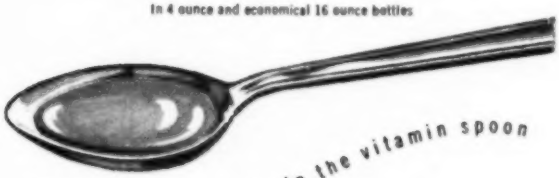

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The Ammoniacal Diaper. Simplicity and Economy.
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1. Anderson, H. C., and McCarty, M.: Am. J. Med. 8:445 (April) 1950.
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*Shwachman, H., Children's Hospital, Boston, The Child in Health and Disease, Grulee and Eley, 2nd Edit.

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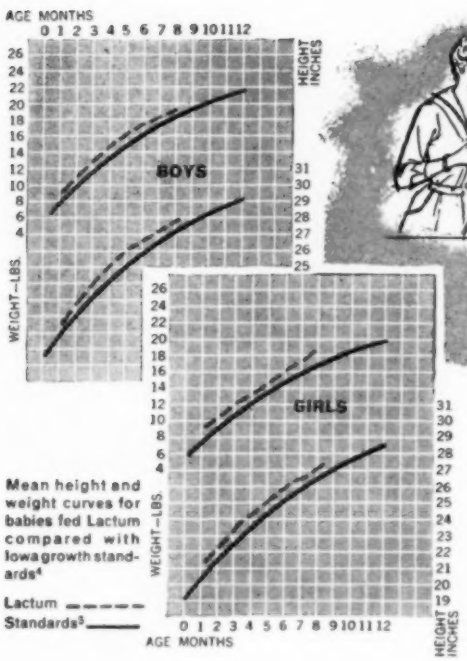
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1. Jeans, P. C., in A.M.A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, p. 275; 2. Albanese, A. A.: Pediatrics 8: 488, 1951; 3. Holt, L. E., Jr., and McIntosh, R., in Holt's Pediatrics, ed. 12, New York, Appleton-Century-Crofts, Inc., 1953, pp. 175-178; 4. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585, 1951; 5. Jackson, R. L., and Kelly, H. G.: J. Pediat. 27: 215, 1945.

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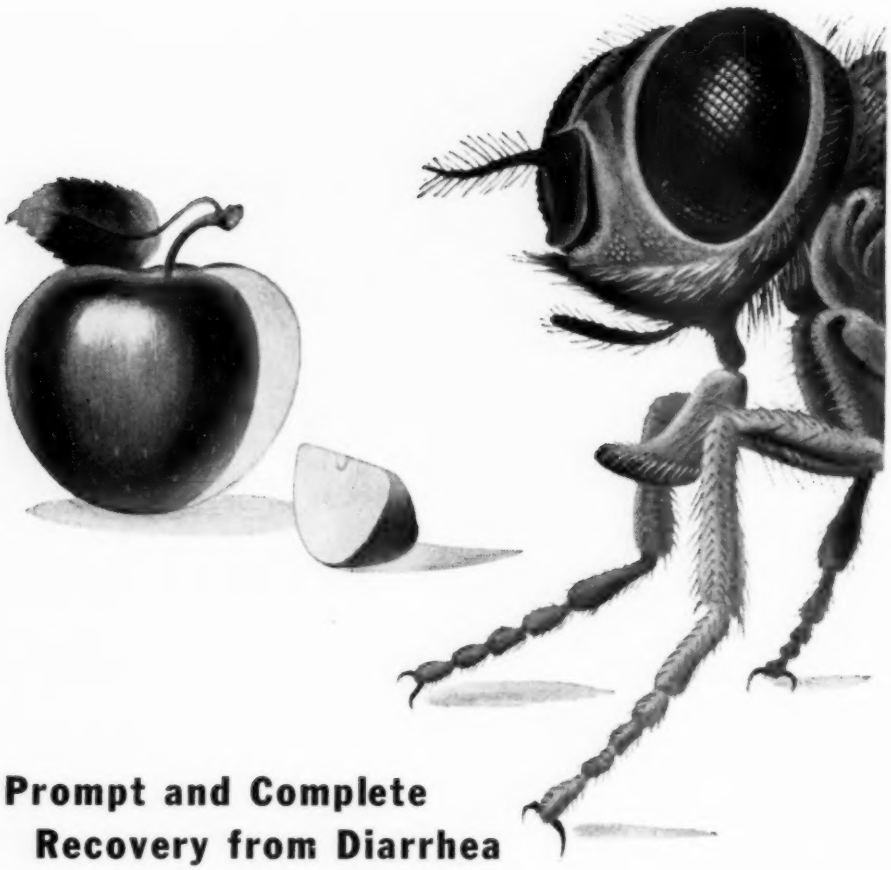

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1. Russ, J. D.: Personal communication

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USE OF A NEW ANTICHOLINERGIC SOLUTION (ANTRENYL BROMIDE) IN PEDIATRICS

ELMORE M. FIELDS, M.D.
Hempstead, N. Y.

The ability of the anticholinergic drugs to inhibit gastrointestinal motility in small doses led to the assumption that this type of compound could prove of value in certain pediatric conditions.

Our interest was aroused in one of these anticholinergics, Antrenyl Bromide, which had proved to be clinically effective in peptic ulcer, hypertrophic gastritis and other spastic conditions of the gastrointestinal tract.[1]

Rowen, Bachrach, Halsted and Schapiro[2] found that Antrenyl Bromide has a definite inhibitory action on the motility of the esophagus, stomach, small intestine and colon. The effect varied in degree and duration, depending on the type of motility, level of the gastrointestinal tract involved, dosage and route of administration.

Pharmacologic studies demonstrated that the action of the drug was highly specific against acetylcholine.[3] In addition to such anticholinergic action, the compound had a definite but more transient ganglionic blocking action. Chronic toxicity studies revealed that Antrenyl produced no pathologic changes in the tissues.

In experiments on the suppression of ulcer formation in the Shay rat, Antrenyl Bromide provided greater protection than menthantheline or atropine.[4]

METHOD

An Antrenyl Bromide solution (1 mg. per drop) for pediatric

use was made available to us for our study.* The solution was used in 120 children with the following disturbances: infantile colic (40), spastic constipation (10), pylorospasm (8), hypertrophic pyloric stenosis (1), cerebral palsy (30), functional enuresis (10), epigastric pain with hepatitis (12), congenital anomalies of the gastrointestinal tract (3), neurogenic colon (2), functional emesis of the newborn (1), cerebral agenesis with functional vomiting (1), and epileptiform crisis (abdominal) (2). The children ranged in age from a newborn infant to 17 years.

In general, the drug was well tolerated in every age group. All the cases studied, with one exception, showed satisfactory clinical improvement. The one exception was a newborn infant with projectile vomiting which began 32 hours after delivery. Although the vomiting persisted, the severity of the emesis did subside somewhat with Antrenyl Bromide, permitting gavage feedings.

The infants and children did not evidence either hyperexcitability or sleeplessness. There were no hypnotic effects from the drug. Antrenyl Bromide Solution seemed to encourage relaxation and improve sleep and emotional behavior.

Only eight patients (6.6 per cent) showed any intolerance to the drug and then only to a mild degree. Of these eight, six were infants (colic group) with allergic backgrounds who developed atropine-like flushes with a dose of three drops. One cerebral palsy girl developed diarrhea and one cerebral palsy boy developed an atropine-like flush. Reduction in dosage (case report 5) eliminated both side effects.

CASE REPORTS

1. Four-week-old male, with clinical signs of pyloric stenosis, including projectile vomiting and 12 hour retention of barium meal. Patient was started on Antrenyl, using 1 drop q.i.d. before meals, increased to 3 drops q.i.d. by the end of 3 days. On thick cereal with Antrenyl, emesis subsided by the fourth day. There was no evidence of abnormal peristaltic waves and the retention of barium was reduced to 5 hours. Antrenyl was continued for 2 weeks. At the end of 1 week, the child gained rapidly. Clinical

*Antrenyl Bromide Solution for pediatric use was supplied by Ciba Pharmaceutical Co., Summit, N. J.

improvement was very satisfactory. Complete improvement was noted at the end of the second week.

2. Forty patients, 20 boys and 20 girls, ranging in age from 5 days to 16 weeks, had a history of severe abdominal colic with restlessness, irritability, tension and irregular bowel function. All these children with infantile colic also had a familial history of allergy. Ten children required soybean derivatives or goat's milk and dietary control.

Antrenyl was the basic drug; the dose averaged from 1-3 drops and was given 15 minutes before feedings. Duration of treatment varied from 10 days to 8 weeks. The average patient responded satisfactorily within 5 days. Relief from pain and restlessness was apparent. The patients were able to take large quantities of food and were more satisfied. Period of sleep was increased up to 6 hours at night.

3. Eight children (3 females and 5 males), ranging in age from 3 years to 12 years, presented a history of severe epigastric pain following meals (resembling the adult ulcer patient). Gastrointestinal series revealed pylorospasm, functional in type. Antrenyl, in an average dose of 3 drops t.i.d.a.c., was given over a 6 week period. Results were satisfactory in 6 patients and 2 patients were measurably improved.

4. Ten patients (6 females and 4 males), complaining of severe abdominal pain, constipation and nausea. These children, whose ages ranged from 2 to 10 years, were typically unstable emotionally with a background of parental anxiety and poor social and school adjustment. The history of spastic constipation appeared to be directly related to an escape mechanism for avoiding environmental changes. The average dose of Antrenyl was 3 drops 3 times a day before meals. Treatment was continued for an average of 4 weeks. Decided improvement was noted in the patients.

5. Thirty patients with cerebral palsy: 15 boys ranging in age from 2 months to 12 years, 15 girls ranging in age from 3 weeks to 17 years. Rigidity and spasticity with lack of muscle control, ataxia, and athetosis were dominant in these children. There was excessive salivation, bowel dysfunction, inability to coordinate and retardation in speech. Antrenyl was started specifically to determine whether the excessive salivation could be controlled and some degree of muscle relaxation obtained.

The dose of Antrenyl was increased to an average of 5 drops in those children 10 to 13 years old. Tolerance to the drug was good in all the children except two—one had atropine-like flushing, the other diarrhea. Reduction of the dosage from 5 to 3 drops in these two children eliminated the side effects.

At this writing, the children have been under treatment for six months. The over-all clinical picture is most encouraging. About 25 of these children have had a reduction in salivation and have obtained adequate muscle control and relaxation. Active and passive exercises can now be given more readily.

6. Ten children with enuresis (five boys and five girls ranging in age from 4 to 12 years) gave a history of emotional immaturity. There were no organic abnormalities. Other general treatment for control of enuresis was unsatisfactory.

They were started on Antrenyl in average doses of 3 drops t.i.d., with the last dose given at bedtime; duration of treatment was 6 weeks. These children are still under observation but the treatment appears to be relatively successful.

7. Twelve patients from 3 to 13 years with clinical signs of hepatitis following onset of adenopathy with malaise, anorexia and change in bowel function (most often constipated) obtained relief, from abdominal distress, with Antrenyl within 48 hours. Blood count, chemistries and agglutination tests confirmed the diagnosis of mononucleosis with hepatitis. The average duration of treatment, using 3 drops of Antrenyl t.i.d.a.c., was 10 days.

CONCLUSION

A new drug, Antrenyl Bromide Solution, for pediatric use in various spastic disturbances of the gastrointestinal tract, enuresis and in cerebral palsy, was studied in 120 infants and children. The drug was found to be effective and safe.

An average dosage of 3 drops t.i.d. appeared to be sufficient to achieve satisfactory clinical improvement.

Further study is warranted.

SUMMARY

1. The effect of a new anticholinergic drug, Antrenyl Bromide Solution, was studied in various spastic disorders and enuresis in infants and children. The age of these patients ranged from a newborn to 17 years.

2. One hundred nineteen of 120 children studied demonstrated satisfactory clinical improvement with Antrenyl Bromide Solution.

3. Only 8 patients (6.6 per cent) evidenced any intolerance to the drug and then only to a mild degree (flushing, diarrhea).

4. The drug appeared to encourage relaxation, improved sleep and emotional behavior.

5. Antrenyl Bromide Solution should prove to be an excellent adjunct in the treatment of certain pediatric disturbances, particularly gastrointestinal spasms and in cerebral palsy.

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PERISTALTIC HORMONE IN NEWBORN INFANT. (Rev. Asoc. méd. argent., 67:463, Nov. 15-30, 1954). The subject of this report was admitted to the hospital five days after birth with a possible diagnosis of intestinal obstruction or pylorospasm. The infant weighed about 2,721.55 gm. During the five days of his life, he vomited material containing bile whenever he was fed and did not pass meconium. He was fed through a duodenal tube, but the vomiting continued. A rectal tube was passed frequently without obtaining meconium. At roentgen examination, the small intestine appeared to be patent and the colon showed normal filling after an enema. The patient was given 228 mg. of dried extract of peristaltic hormone at intervals of 24 hours for two consecutive days. Shortly after the first dose, the patient showed tolerance to food, and a little later he had the first bowel movement. Feeding and passage of feces became normal during the two days of the treatment and continued so after its discontinuation. The patient was discharged two weeks after discontinuation of the treatment. This is the first case in the literature of administration of peristaltic hormone to a newborn infant. The dose of the peristaltic hormone for the newborn is about 100 mg. for each kilogram of body weight. The tolerance to the drug is good and results satisfactory.—*J.A.M.A.*

EXPERIMENTS WITH COLLODION CAPSULES FOR IMMUNIZATION AGAINST POLIOMYELITIS AND OTHER INFECTIONS*

FREDERICK M. ALLEN, M.D.
New York.

(*Continued from August issue*)

BACTERIA. TUBERCULOSIS

Collodion capsules were filled with growth of tubercle bacilli scraped from the surface of solid medium together with a little of the medium itself. They were implanted either subcutaneously or intraperitoneally in mice, guinea pigs and rabbits. The capsules for mice were approximately 0.6-0.8 cm. long and 0.3 cm. thick. Those for guinea pigs were about twice as large, while those for rabbits were still larger and variable, some of those in the peritoneum measuring as much as 3.5 x 1.2 cm. All the capsules healed smoothly in place and were surrounded by the usual tissue envelope. In contrast to injections of the bacilli or their products, there was no sign of local irritation or systemic illness. The only exception pertains to the intraperitoneal capsules in mice, which occasionally give rise to weakness and ill health evidently due to adhesions or other mechanical obstructions and no different in the case of these or other organisms. Mice showing this weakened state must be excluded from the resistance tests. There still remains a suspicion of slight disturbances of health which may make mice less dependable than the larger species. Bacilli survived in the capsules for the several weeks of sojourn in the body, as proved by cultures from the capsule contents, but the growths gave the impression of a decrease rather than an increase in numbers. The strains of bacilli used for both the capsules and the test injections had been certified as highly virulent. The challenge doses were not measured according to methods in the literature. They consisted of growth from solid media made into a uniform suspension in salt solution, so that doses for the compared animals were identical but not related to those used by other writers. The suspensions were almost milky and the dosage heavy.

*From the City Hospital, Welfare Island, New York, N. Y.
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Mice which received the capsules and which escaped accidental death or disqualification numbered 38. Five weeks after implantation the capsules were removed. After allowing 1 week for recovery from the operation, 0.1 cc. of a heavy suspension of human tubercle bacilli of the H37Rv strain was injected subcutaneously in a hindleg of each test mouse and a corresponding control. As there were no grossly noticeable results, 24 days later similar injections of 0.2 cc. were given intraperitoneally. The animals all died within the next 3 weeks, with gross lesions of tuberculosis in the lungs, seldom in the abdominal organs. Some test animals died earlier than some of the controls, but the average survival of test mice was about a week longer than that of the controls. This is a rather high fraction of the total survival, but more detailed analysis is unprofitable because of the small number of animals and especially the overdosage, which proved fatal too early and tended to overwhelm any resistance created by the capsules.

At the same time, a dozen mice were injected intraperitoneally with the Calmette-Guerin bacillus. The dosage was so heavy that 4 of the mice died within 2 weeks. The others recovered full strength, and after 6 weeks they were tested with H37Rv injections like the above-described mice. Protection was evident, in harmony with reports in the literature,[13] for with one exception the vaccinated mice lived longer than their controls. The difference in survival between the vaccinated and the capsule-bearing mice was slightly, but perhaps not significantly, in favor of the latter.

The Ravenel strain of bovine tubercle bacilli was used for rabbits. As a preliminary, 4 rabbits were tested after removal of subcutaneous capsules which they had carried for 3 weeks, by injecting 0.1 cc. of heavy suspension of bacilli from solid medium subcutaneously in an ear, for possible differences in either local reaction or systemic invasion. Long-lasting caseous abscesses resulted, with ulceration, but there were no striking or obvious differences between test animals and controls.

The main experiments were performed on 8 rabbits, each of which carried capsules for periods of 5 to 9 weeks, and 4 controls. As no differences were noticed between those having subcutaneous or intraperitoneal capsules, they are not separated. Two weeks after removal of the capsules, all the animals were given 0.3 cc.

of a heavy suspension of Ravenel bacilli intraperitoneally. The 4 control rabbits died in 39 to 60 days. They included one animal which, instead of being matched, was chosen as being decidedly larger and stronger than any of the test rabbits. The rabbits which had had capsules died in periods of 55 (1 animal) to 89 days. There was no distinction in the autopsy findings of test and control animals; peritoneal lesions were usually prominent and the lungs were solid with tubercles.

An observation was undertaken on 2 additional rabbits which were given their infecting doses while the capsules remained in place. Accidents prevented determining the actual survival time, but at least it was not shortened and there was no obvious harm from the continued presence of the capsules. A fuller investigation would have been desirable regarding the influence of capsules in the presence of active infection.

Capsules filled with the human H37Rv tubercle bacilli were implanted in 6 guinea pigs, 2 or 3 to each animal, generally 2 subcutaneously and 1 intraperitoneally. Like the rabbits, guinea pigs tolerate capsules excellently without signs of either mechanical or toxic disturbance. After 6 weeks the capsules were removed surgically. The animals, then weighing 350 to 500 gm., were matched with 4 controls of similar weight, and all received intraperitoneal injections of 0.2 cc. of a rather milky suspension of the H37Rv bacilli. The controls died in 38 to 53 days. Four of the test animals died in 65 to 79 days, and one in 114 days, all showing typical tuberculous lesions. The one remaining animal lost weight and appeared somewhat unwell during the first 6 weeks, then regained normal appearance, and was fat and strong when killed for autopsy after 6 months. All organs were free from grossly discoverable tuberculosis except for two split-pea nodules at the base of the right lung, which were very hard and were probably fibrosed tubercles.

The rather important question of the influence of capsule size or the length of time they are carried could not be investigated. The abundance of capsules in the foregoing experiments will be noticed. In only one guinea pig a single spherical capsule of only 0.5 cm. diameter was implanted subcutaneously, and death occurred within the time limits of the controls. Though large size seems favorable, the results do not entirely exclude the possibility that

a capsule of minimum size may confer some protection if carried for a sufficiently long time.

Two guinea pigs received intraperitoneal injections of a heavy suspension of Calmette-Guerin bacilli, without apparent disturbance of health. One month later they were given 0.2 cc. of H37Rv suspension, in series with the animals that had had capsules. They died in 48 and 59 days, respectively, i.e., barely beyond the time limits of the controls.

Though cost precluded using a desirably large number of animals of the larger species, the aggregate experience with the three species was in favor of a protective influence of the capsules, perhaps superior to that of the BCG vaccination.

TRYPANOSOMES

The present dependence is upon drugs for both treatment and prophylaxis of trypanosomiasis. Attempts at immunization of animals have not been entirely negative but still have yielded nothing practical.[14] The wave-like course of the infection in man and large animals, with exacerbations and remissions and appearance and disappearance of swarms of circulating flagellates, supports the theory of changes in the antigenicity of the organism, so that by the time the body develops immune substances against one form there is an emergence of new resistant forms.[15] If the host does not die from the protracted struggle, the natural disease is followed by immunity against the strain of the organism which caused it but not against slightly different strains. Inasmuch as flagellates have been found to grow in collodion sacs with provisions for dialysis *in vitro* even more abundantly than in ordinary cultures,[16] there seemed to be a reasonable chance that they might flourish perhaps even better *in vivo*, so that diffusion products might give rise to antibodies against all possible variants of one or several strains of the organism during the long time they are thus harbored in the body without being able to invade.

Some experiments were begun with T. cruzi, which proved insufficiently lethal for the purpose. T. gambiense was carried through successive passages by intraperitoneal injections of tail blood from infected animals mixed with salt solution. This infection is fatal in 100 per cent of rats and mice. The doses were empirical, without counts of organisms, but, by using graded

injections in each series, the time of survival was varied and the deaths of the first animals furnished guidance in dealing with the others. Under these conditions the survivals of rats ranged between about 5 and 14 days. Mice were also used for both capsule tests and controls, but as their survival time is shorter, they tolerate capsules less perfectly, and the results are merely confirmatory of those in rats, the present description is limited to the rat experiments.

Approximately 100 rats received capsules subcutaneously or intraperitoneally. They healed and acquired tissue coverings without signs of irritation. They were filled variously with infected rat blood, liver or spleen tissue, sometimes with additions of salt solution, glucose, gelatin, agar, or several kinds of bacterial cultures. These variations were tried because of disappointingly poor survival of the trypanosomes. Sometimes drying of the capsule contents indicated lack of diffusion. Under any circumstances after 2 weeks there was absence of motile organisms and of infectivity.

The T. gambiense infection is remarkably dependable in that rats receiving identical inoculations die quite uniformally on the same day, never much more than 24 hours apart. Ths same uniformity prevailed between test animals and controls. Besides different ways of preparing the capsules, attempts were made to counteract the dying out of the trypanosomes by inserting one subcutaneous and one peritoneal capsule every 2 weeks, so that after 4 weeks the rat was carrying 6 capsules. There was never the slightest sign of immunization or protection.

This failure may possibly be technical. As there was the difficulty of making capsules sufficiently impermeable to hold the poliomyelitis viruses, there may be here the opposite problem of sufficient diffusion for trypanosomes. In fact, the hope at first was that the capsules providing free exchange with body fluids might be a more convenient means of keeping trypanosomes than either artificial culture or continuous passages through animals. Results may perhaps be transformed by a suitable culture medium in the capsules instead of the materials used in these trials. If the organisms can thus thrive, as they have been found to do in collodion sacs *in vitro,* the expectation of an immunizing action seems reasonable. The problem is extremely important because try-

panosomiasis is one of the great world scourges of man and animals, and no biological protection method exists. Animal husbandry may perhaps be a source of independent financing for such a research.

SPIROCHAETES

Cultures were obtained of Leptospira icterohemorrhagiae, canicola and pomona. Capsules filled with the liquid were implanted in young guinea pigs subcutaneously and intraperitoneally. Healing has occurred readily without signs of irritation. But the initial experience has been that the organisms die out in a few days, so that protection experiments appear unpromising unless some way is found to prolong the survival.

DISCUSSION

The poliomyelitis group being, together with the foot and mouth disease virus, the smallest infectious agents known, the problem of their escape through faulty capsules was not solved. As already mentioned, the pore size of Elford's gradocol membranes furnishes a recognized standard measure for various kinds of particles. Thus, it has served for comparisons of the diameter[17] of the egg albumin molecule, about 4 mμ, the poliomyelitis virus, 8-12 mμ, and larger viruses ranging from about 25mμ for yellow fever or encephalitis to as high as 150 mμ for rabies.* Presumably

*Since this paper was written, Schwerdt[18] and co-workers have published impressive studies with the electron microscope showing that the poliomyelitis virus is a sphere with a diameter of 28 mm. Also the writer has learned of early experiments by Jungeblut,[19] in which collodion sacs containing poliomyelitis virus were implanted intraperitoneally in several monkeys. Permeability tests of these sacs showed that they were freely permeable for methylene blue, they allowed passage of small quantities of congo red, and they retained prussian blue. Nevertheless, the early records in the light of the present work indicate clearly that virus escaped from these sacs. Therefore the above statement of the small size of the poliomyelitis virus remains correct as regards the essential feature of the present work, namely the passage through collodion.

Attention should be given to this conflict between electron microscope measurement on one hand and gradocol estimates and infectivity experiments on the other. If unexplained, it may cast doubts on measurements of other viruses. It might be supposed that filtration pressure can deform the virus particle so as to force it through a small gradocol pore. This fails to account for the passage through capsules without pressure, freely and continuously, as proved by the deaths of many successive animals. Does this imply an unsuspected ability of a virus to distort its substance "spontaneously," like a leukocyte, to pass through a small opening? If a comparison be made with bacteriophage, does the grouping of such a virus around a bacterium suggest purely accidental dispersion or something like chemotaxis and motility? Such a speculation still could not explain results of the writer's abortive attempts to prepare a vaccine by collodion filtration, in which the virus passed through rather thick membranes which had only water or salt solution on both sides. Is the virus inherently disposed to wander by diapedesis or otherwise, and may it thus spread among nerve cells by another process than passive transport by blood or lymph? Or will more thorough search reveal viable material smaller than the visible virus? If these are all empty guesses, there still remains the need for an experimental explanation of the discrepancy between membrane passage and electron microscope measurement.

the retaining of larger viruses should be simple, but for the smallest viruses there is as yet no demonstration of capsules meeting the demands of safety, uniformly free from flaws and not permitting escape of a single virus particle. An affirmative view is encouraged by the fact that a considerable thickness of collodion is permissible, and an appreciable number of efficient capsules were prepared under the crude conditions of these experiments. One incidental point may turn out to be most important if it can be confirmed and applied, namely, the evidence that immunization is obtainable with the diffusion products of the virus, not denatured by heat or chemicals (formaldehyde), and does not require the presence of either living or dead virus particles. If either killed or modified viruses prove unsatisfactory in the current large-scale trials, possibly a third form of vaccines, namely a filtrate, may provide both effective and durable immunity.

The basic concept of the use of capsules, namely, to permit fully virulent organisms to have lodgment in the body without being able to invade, was justified in the immunization of mice against the Columbia SK virus, which has never been accomplished before and the possibility of which with vaccines is questionable. Against the apprehended inconvenience of the subcutaneous insertion of a capsule, three hopes have been entertained: the capsule may perhaps not need to be carried long; the immunization may perhaps be strong and life-long like that from the natural disease without the dangers or reactions of either the disease or ordinary vaccination; and one capsule may serve against several kinds of infection. If other methods fail, patients may readily accept this in preference to the danger of poliomyelitis, espcially if immunization is completed in two or three weeks. As for other organisms, those which produce a strong diffusible toxin are obviously to be excluded. It is a permissible hope that the neurotoxic and other dangers of rabies, yellow fever and other vaccines may be obviated by capsules. The idea of life-long immunization against smallpox without local inflammation by means of capsules of cowpox or actual smallpox virus was discouraged by the unexpected local reaction against capsules of Rickettsia, and evidently tests of each organism must decide. Also, some organisms which are known to produce immunity have not produced it in capsule experiments, so that it is necessary

either to accept limitations of the method or find ways of improving it. The peculiar fact that, as far as observed, the development of immunity does not result in killing the organisms in the capsules, may emphasize the role of cells in destroying invaders or may call for some other theoretical explanation, such as the specia[l] influence of collodion on toxins or interfering substances.[5]

In the important field of tuberculosis, the few observations of increased resistance with capsules have seemed encouraging. But, though the glandular enlargements and occasional more severe reactions from BCG vaccination may be avoidable by capsules, the weight of recent evidence favors the effectiveness and general harmlessness of this vaccination, so that replacement of it seems questionable unless a superiority of capsules is proved under special conditions. One such condition may be the presence or suspicion of incipient infection, and the unsettled question of the action of capsules with existing tuberculosis may deserve investigation. A bolder possibility, namely, of using capsules in treatment of active tuberculosis, remains speculative. A more definite prospect is that the lepra bacillus may remain alive or multiply in implanted capsules, and may thus provide better prophylaxis against leprosy than BCG vaccination or other known means.

The observation that various bacteria do not impair the effectiveness of capsules of Columbia SK virus during months of implantation in mice encourages the original hope that one capsule may serve for several purposes. Granting necessary tests to rule out possible interferences, a hypothetical capsule for children under average conditions in the temperate zone might contain the three principal strains of poliomyelitis, the viruses of measles and mumps and the bacillus of whooping cough. In view of the lack of prejudice against implants of hormone pellets or tissue fragments, it is surprising if the insertion of a capsule for a limited time appears unthinkable. Even if never adopted clinically, the method may still prove useful in some infections of animals.

SUMMARY AND CONCLUSIONS

1. The general idea has been stated as the lodgment of virulent organisms where they can have the freest possible diffusional interchange with the body but cannot invade.

2. The implantation of collodion capsules filled with infected

mouse brain has induced the first immunization of mice against the Columbia SK virus, though not against intracerebral inoculation or against unlimited peripheral doses.

3. The same method apparently immunized mice against intracerebral inoculations of MEF virus, but again dosage was a factor and the protection was not unlimited.

4. The following additional details were noted in these experiments.

(a) The problem of making collodion capsules thoroughly secure against escape of these extremely small viruses was not solved, but a solution appears theoretically feasible. Such a difficulty does not exist with larger organisms.

(b) Paralytic deaths among mice with MEF capsules, comparable to those among the Columbia SK series, required the hypothetical assumption of infection by continuous seeding of virus from faulty capsules. This explanation seemed to be supported by the observation that mice, which are known to resist single peripheral MEF injections, can be infected by repeated subcutaneous injections. This result is stated with reservations as to possible error, to be checked by investigators with the necessary serological technique. If valid, it suggests an epidemiological influence of repeated exposures.

(c) The results with capsules, especially with the SK virus, prove that immunity can be induced by a filtrate of unaltered products from the virus, not containing either living or dead virus particles. The potency of such a filtrate in comparison with conventional vaccines remains to be determined.

5. Complete failure of immunization by capsules was encountered with the Rickettsia of scrub typhus and the trypanosome of African sleeping sickness. The Rickettsia caused unexpectedly strong local irritation, and tests of other organisms must consider this possible factor. It is uncertain whether technical improvements might alter the failure in the important problem of trypanosomiasis.

6. Capsules containing tubercle bacilli are tolerated without signs of local irritation or systemic illness. The degree of protection observed in a few animals bears favorable comparison with that from BCG vaccination. Besides medical or veterinary tuberculosis,

there is a more remote possibility of the use of capsules of lepra bacilli for prophylaxis of leprosy.

7. Persistence of high infectivity of mouse brain in capsules in animals' bodies for 4 to 6 months sets a record for preservation of the Columbia SK virus at this temperature, especailly in the presence of bacteria. It is questionable whether something in the interchange with body fluids favors maintenance of the virus. This experience supports the possibility, as yet unproved, of counterbalancing the inconvenience of capsules by using mixtures for simultaneous immunization against several organisms, excluding those with dangerous diffusible toxins.

FOOTNOTE. The Columbia SK virus and also the mouse-adapted MEF virus were kindly supplied by Dr. C. M. Jungeblut. The Rickettsia tsutsugamushi was obtained from the Army Medical Service Graduate School at Washington, D. C., Trypanosoma cruzi from the Communicable Disease Center at Chamblee, Georgia, and T. gambiense from the National Microbiological Institute at Bethesda, Maryland. Thanks are due to Miss Sara Scudder, chief bacteriologist at City Hospital, for all the bacterial culture and staining work mentioned in the paper, and for providing the following organisms: Leptospira from the New York City Health Department, and the several strains of tubercle bacilli from Ciba Pharmaceutical Products, Inc.

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1031 *Fifth Avenue*

THERAPY OF HYDROCEPHALUS IN TUBERCULOUS MENINGITIS. (Kinderärztliche Praxis, Leipzig, 21:481, Nov. 1953). Despite progress in treatment by chemotherapeutics and antibiotics, it is often impossible to arrest tuberculous meningitis during the exudative stage. During the chronic state the normal relationship between production and resorption of the cerebrospinal fluid often becomes impaired, and a more or less severe hydrocephalus results. On the basis of four case histories, which were selected from a large number, Janssen and Wilms show how difficult it is to make a prognosis. The children were in a comatose state, most of them for months and one for more than half a year. They had to be fed by tube. Choked disk and other clinical signs indicated the presence of hydrocephalus, which was so severe that there was little hope that life could be preserved. It seemed that mental and physical defects would result even if death could be prevented. After temporary interruption, treatment with streptomycin was resumed, however, and the child eventually recovered without mental defects, although hearing was defective. Results obtained in the other three cases were similar. The authors advise great caution with regard to surgical interventions for hydrocephalus, because they found that such treatment was ineffective in several cases and treatment with antibiotics may arrest hydrocephalus even in chronic cases of tuberculous meningitis.—*J.A.M.A.*

CLINICAL STUDIES ON THE EFFECT OF METHYL-ANDROSTENEDIOL THERAPY IN INFANCY AND CHILDHOOD

S. Awwaad, M.D., D.Ch.
Assistant Prof. of Pediatrics, Abbassia Faculty of Medicine, Cairo, Egypt

The problem of growth retardation in infancy and childhood is of paramount importance to pediatricians, being an everyday complaint in both special clinics and general hospitals. Hence the great interest with which we meet medicaments that are expected to influence child growth.

Certain vitamins and hormones are known to promote growth. Vitamins in this respect act mostly through improving the appetite. Though they are, generally speaking, safe to give, yet more often than not we have been disappointed with them. Recently vitamin B_{12} has raised great interest as a growth promoting factor. This followed the work of Wetzel (1949, 1952) and Chow (1951). Downing (1950), however, failed to get acceleration of growth in premature infants with B_{12}.

Of the hormones, the growth hormone of the pituitary, insulin and androgens are known for their anabolic effect. Although the growth hormone fulfills the criterion of tissue growth in animal experimentation, and is devoid of androgenic activity, market preparations of this hormone have been disappointing. Insulin is frequently used to increase weight, but this increase is mainly the result of fattening the patient and not through growth of his tissues.

It has long been established that testosterone propionate causes a retention of nitrogen and other tissue building elements in human beings. The growth promoting effects of testosterone compounds were first demonstrated by Kenyon and his associates (1940). Their observations suggested the possible therapeutic value of using the androgens to promote protein anabolism in conditions of debility and retarded growth; unfortunately their usefulness in this respect was limited by their undesirable androgenic side effects. For this reason, efforts were made to search for steroid compounds which would have the anabolic properties of testosterone without its androgenic side effects. Among the compounds so studied is methylandrostenediol (MAD), which was first synthesized by Ruzicka, Goldberg and Rosenbergin in 1935.

The reports on the relative anabolic and androgenic effects of this compound show a lot of controversy. Wilkins and Fleischmann (1946), using it in a daily dose of 30 mg. orally, failed to get any effect on the patients' growth or ability to gain weight. Homburger and his associates (1950), in a preliminary report, suggested that MAD is a non-virilizing steroid hormone with moderate protein anabolic effect. In rats, Gordan and his associates (1951) found that it has a myotrophic potency comparable to that of the androgens in the same dose of 1 mg. per Kg. and that its androgenic activity was lacking with that dose and only appeared with a dose of 50 mg. per Kg. In a further study on human subjects Homburger and his associates (1953) obtained with MAD significant protein anabolic effect with occasional mild virilization. Partridge and his associates (1951), however, after a study on the metabolic and clinical effects of MAD in human subjects, concluded that probably in doses sufficient to produce growth promoting effects, significant androgenic effects also occur. Homburger and his associates commented on this observation that the contradiction is only an apparent one as the cases of Partridge et al. were relatively young and were so notoriously more sensitive to virilization.

The present work is a further study to evaluate the effect of MAD therapy as a growth promoting factor in infants and children and to determine whether in doses sufficient to cause significant increase in weight and androgenic effect will also be noted. This point is especially important, as our cases normally produce but little androgens and might presumably be especially sensitive to the medication administered.

Fifteen cases of infants and children, varying from 2 months to 7 years of age, were given the compound.* They were all free from any serious organic disease which might affect their growth. Their main condition was essentially debility, wasting and underweight with marked loss of appetite. Iron, vitamins and various tonics were given to the cases under investigation for several months before MAD therapy, with no result.

The drug was given intramuscularly, as the patients were too young to keep the linguets under their tongues. The duration of treatment varied from 2 to 18 weeks. In 4 cases, after a course

*The drug used in this study is protandren "Ciba." It is a microcrystalline watery suspension in vials of 10 cc., each cc. containing 50 mgms. of methylandrostenediol

TABLE I

Case No	Name	Sex	Age (yrs)	Dose and Frequency	Duration of tt. in weeks	Weight in kilos	Height in cms.	Increase in wt. in kilos	Increase in height in cms.	Side Effects	Remarks
1	M.M.	M	7	25 mg. twice/wk. (= 1.5 mg./kg.)	12	17 (23)*	118 (122)*	2.25 (0.5)*	2 (1.5)*	Nil	.....
2	A.Z.	M	1.5	25 mg. twice/wk. (=2.8 mg./kg.) last dose to 50mg.	18	8.8 (11.5)*	73 (77)*	1.5 (1.1)*	5 (4)*	a sterile abscess followed the last dose	4 months continuous tt. without androgenic side effect.
3	N.F.	F	2	25 mg. twice/wk. (=2.5 mg./kg.)	9	9.75 (13)*	80 (83)*	1.5 (0.3)*	2.25 (1.5)*	Nil	.....
4	S.A.	F	6/12	10mg. twice/wk. (2.2 mg./kg.)	3	4.6 (7)*	59 (62)*	1.2 (0.5)*	2.25 (1.5)*	Nil	.....
5	Z.A.	F	5	30 mg. twice/wk. (2 mg./kg.)	2	15 (19)*	108 (110)*	1.0 (0.1)*	0.50 (0.25)*	Nil	.....
6	S.B.	F	3	25 mg. twice/wk.	8	12 (15)*	88 (92)*	2.0 (0.3)*	2.0 (1)*	Nil	In 4 months rest added 1/4kg.
	S.B.	F	3½	25 mg. 3times/wk (2 mg./kg.)	3.5	14.25(16)*	91 (96.5)*	1.0 (0.1)*	1.0 (0.5)*	Marked enlargement of Clitoris & some growth of Pubic hair.	.....
7	Th.F.	F	2	25 mg. twice/wk.	7	9.1 (13)*	80 (83)*	1.47 (0.3)*	2.25 (1.5)*	Nil	In 4 months rest added 1/4kg.
	Th.F.	F	2.5	25 mg. 3times "	4	10.75 (14)*	82.25 (87.5)*	0.75 (0.1)*	1.0 (0.75)*	Marked enlargement of Clitoris	
8	O.S.	M	2.5	25 mg. twice/wk. (2.5mg./kg.) last dose ↗ to 50 mg.	8	10 (14)*	85 (87.5)*	1.2 (0.3)*	2.0 (1.5)*	Local inflamatory reaction followed the 50 mg. dose.	.....
9	S.S.	F	4	25 mg. twice/wk. (1.6 mg. Kg.)	9	15.5 (17)*	99 (101)*	3.25 (0.3)*	2.0 (1.5)*	Nil	.....
10	H.O.	M	4.5	30 mg. twice/wk. last dose ↗ to 90mg (6 mg./kg.)	9	15 (18)*	102 (105.5)*	2.25 (0.3)*	2.0 (1.5)*	90mg. dose → local inflamatory reaction	.....
11	S.H.	M	2.5	25 mg. twice/wk. (2 mg./Kg.)	9	12.5 (14)*	85 (87.5)*	1.5 (0.3)*	2.0 (1.5)*	Nil	.....
12	A.SH.	F	3	25 mg. twice/wk. 2.5mg./kg.	9	11 (15)*	89 (92)*	1.5 (0.3)*	2.0 (1.5)*	Nil	.....
13	M.Y.	M	2/12	10 mg. twice/wk. 3 mg./kg.	3	3.3 (5)*	49 (54)*	1.6 (0.6)*	2.0 (1.5)*	Nil	.....
14	S.F.	F	5	25 mg. twice/wk.	9	15 (19)*	106(110)*	2 (0.3)*	2.0 (1)*	Nil	In 4 months rest added 1/5kg.
	"	"	5½	" " " (1.5mg./kg.) "	8	17.5 (20)*	109(113)*	1.5 (0.3)*	1.5 (1)*	Nil	
15	K.H.	F	3	25 mg. twice/wk.	9	12.5 (15)*	88 (92.0)*	1.5 (0.3)*	2.5 (1.5)*	Nil	In 4 months rest added 1/5kg.
	"	"	3½	" " " (1.6 mg./kg.)	9	14.5 (16)*	91.5(96.5)*	1.3 (0.3)*	2.0 (1.5)*	Nil	

N.B. The figures in between ( )* is the average expected for normal infants and children at these ages.

of 9 weeks treatment with the drug, a period of 4 months rest was given after which a second course was administered. The dose given varied from 1.5 to 3 mg. per Kg., twice or three times weekly. On three occasions the dose was raised to 5 or 6 mg. per Kg. Children were given a liberal diet with plently of proteins. The weight was recorded weekly during treatment and the height was taken at the beginning and at the end of the therapy.

A summary of the cases studied, the treatment adopted and the results obtained is appended in Table I.

DISCUSSION

From Table I, the following points may be noticed:

(1) A dose of 1.5 to 3 mg. per Kg., twice weekly, was well tolerated in all cases. It induced a marked gain in weight and a favorable influence on height with no androgenic side effects. The increase in weight did not differ significantly within this range of dosage, consequently it will be safer and more economic to apply a dose of 1.5 mg. per Kg.

(2) Case No. 2 tolerated a dose of 3 mg. per Kg., twice weekly, for a period of 4 continuous months with no androgenic side effects. In spite of this high dosage, however, his weight gain was less marked than in other cases.

(3) In attempting to accelerate the growth, the dose was doubled in three children (0.5 to 0.6 mg. per Kg.). In one of these a sterile abscess developed after the first injection and in the other two cases a local reaction at the site of the injection appeared and for this reason doubling the dose was given up.

(4) The increase in weight induced with treatment almost ceased once the drug was stopped as it could be observed from the follow-up in cases No. 6, 7, 14 and 15. In these cases, increase in weight during the 4 months which followed the cessation of treatment did not exceed ¼ Kg.

(5) For this reason a second course was tried with these 4 cases to see if growth will be resumed again on readministering the drug. In this second course the drug was given to 2 cases three times weekly for 4 weeks and twice weekly to the other two cases for 8 weeks. It is noticed that the increase in weight started again in all the 4 cases. In the first 2 cases, however, to whom the drug

was administered 3 times weekly, a distinct increase in the size of the clitoris was observed and for this reason the second course was stopped after 4 weeks, hoping for regression of the size of the clitoris during the period of rest. In one of these cases, during the period of rest, some growth of the pubic hair was observed. In the other two cases, to whom the drug was given in the second course twice weekly, no side-effects were observed.

It seems that the side-effects that appeared in the first two cases were the immediate result of the administration of the drug in frequent doses. It is probable that the frequent injections formed a local depot from which the drug, after cessation of treatment, continued to be liberated to the circulation and resulted in the growth of the pubic hair. For this reason the writer is of the opinion that the injections should be more spaced and should not exceed two per week in order to insure the good results of the drug without its undesirable side-effects, and, in older children, for this reason, recommends giving the drug as linguets instead of giving it as injections.

SUMMARY AND CONCLUSIONS

Methylandrostenediol therapy was tried in 15 cases of retarded growth in infants and children. The results, as regards weight, gain, were excellent. The height was also favorably influenced.

The following observations were noticed:

(1) Increase in weight was distinct and constant in all cases during the administration of the drug.

(2) The growth ceased on stopping the treatment.

(3) Growth restarted again on readministering the drug.

(4) The administering of the drug is safe and effective in small doses of 1.5 mg. per Kg., given twice weekly.

(5) On increasing the dose to 5 mg. per Kg., or giving it more frequently than twice weekly, undesirable side effects were observed. These side effects were: (a) Sterile abscess or local inflammatory reaction at the site of the injection. (b) Enlargement of the clitoris and growth of pubic hair.

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CONSTITUTIONAL SIGNS OF ASTHMA IN CHILDREN. (Maandschr. kindgegeneesk., 22:73-84, March 1954). Clinical observations on 187 asthmatic children, who were studied and treated in an Asthma Center, revealed that 82 remained free from attacks after a change in environment. These children had a mild form of asthma. The remaining 105 children with a severe type of asthma continued to have attacks after admission to the center. A correlation could be demonstrated between the frequency of attacks, the clinical symptoms, and the outcome of the tests of pulmonary function. This can probably be explained by the fact that all three are influenced by the narrowing of the bronchioles, which in turn results from infiltration of the mucous membrane with eosinophilic leukocytes. With regard to the pulmonary function, observations on these children indicate that the asthmatic condition improves spontaneously with advancing age; the residual air becomes relatively less and the vital capacity relatively greater. This holds true particularly of the milder forms of asthma. On comparing the children with mild and severe asthma with regard to constitutional factors, it was found that a family history of asthma, eczema, and other cutaneous lesions is more frequent in the severe than in the mild form of asthma. Furthermore, the severe type of asthma usually starts at an earlier age. This seems to indicate that constitutional factors are more important in the severe than in the mild form of asthma.—*J.A.M.A.*

DIETHYLSTILBESTROL — A COCCIDIOIDAL FUNGICIDE*

ROBERT COHEN, M.D.
Bakersfield, Calif.

Curtis and Harrell[1] reported the encouraging use of diethylstilbestrol (a stilbamide derivative) in the treatment of blastomycosis. At the scientific exhibits of the American Medical Association meeting in San Francisco in 1954, the University of Michigan group (Bocobo, Harrell, Curtis and Block) displayed many in vitro studies of antifungal activity of Stilbenes, Nitrostyrene and related compounds. They showed that diethylstilbestrol inhibited coccidioides immitis at 0.01 mgm. per milliliter.

This paper is presented only to confirm their findings before giving it a clinical trial on disseminated coccidioidal cases.

Sabowraud's media with various dilution of diethylstilbesterol were used. The petri dishes were streaked with loops from heavy sinus discharges from a severely disseminated coccidioidal case which were loaded with spherules. The petri dish cultures were read after three days and daily thereafter for three weeks. The controls grew profusely. At 1.00 milligram per milliliter, complete and total inhibition of coccidioides was noted. At 0.5 milligrams per milliliter very small colonies of coccidioides were seen but they did not grow out.

My findings of a 0.99 mgm. per milliliter stronger concentration of diethylstilbestrol, in my estimation for practical purposes, can be considered confirmatory.

The chemical structures of stilbamidine and diethylstilbestrol have a close similarity. I[2] had shown that stilbamidine would inhibit coccidioides. The clincal trials, however, revealed that it did not fare as well in this disease as it did in North American blastomycosis. A death did occur from the use of stilbamidine and I[3] called the profession's attention to its possibility.

This investigator doubts if too high a concentration can be obtained over a long period of time without side effects. However, Curtis and Harrell[1], in their study on two cases of blastomycosis, used only 1 milligram three times a day for a period of relatively

*From the Contagion Section of Pediatric Service, Kern General Hospital, Bakersfield, Calif.

six months. Surely that cannot be considered a large dose. Perhaps it has the impetus to throw the balance in favor of the patients to overcome their infection. Also, I hope that coccidioides will respond to such low doses.

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TO WHAT EXTENT DOES VACCINATION WITH BCG PROTECT AGAINST TUBERCULOSIS? (Monatsschr. Kinderh., 101:517-519, Dec. 1953). During the period from October 1947 to December 1949, 162,865 children between the ages of 3 and 18 years were vaccinated with BCG in Hesse, Germany. This number was selected from 349,181 children who had given a negative reaction to the tuberculin test. Daelen and Dix investigated the occurrence of tuberculosis among vaccinated and nonvaccinated tuberculin negative children in 23 counties in Hesse where 70,424 had been vaccinated and 92,145 had not been vaccinated against tuberculosis with BCG. At the end of four years, 45 cases of tuberculosis had developed among the 70,424 who had been vaccinated and 318 cases among the 92,145 who had not been vaccinated. On the basis of the absolute figures, and after deducting the two cases in which BCG vaccination had been administered during the preallergic phase, the morbidity in those vaccinated with BCG was 0.6 and of those not vaccinated was 3.5 for each 1,000 children observed. Thus the morbidity ratio was 1:5.7 of the vaccinated to the nonvaccinated. The tuberculosis morbidity among those vaccinated with BCG was not greater in large cities, where exposure is much greater, than it was in rural regions, whereas among the nonvaccinated children the incidence of tuberculosis was much greater in the larger cities. For this reason vaccination with BCG should be carried out particularly in the larger cities.—*J.A.M.A.*

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

THE AMMONIACAL DIAPER

JOHN ZAHORSKY, M.D.
St. Louis.

The controversy still continues unabated. How is the strong ammoniacal odor produced? What shall the mother do to prevent the blistering dermatitis on the baby's buttocks? Herewith is a condensation of my original article. (Am. J. Dis. Child., Dec. 1915).

"Fifty years ago I was asked to see a litle girl, 17 months old, suffering from a severe dermatitis of the diaper region. The skin of the buttocks, perineum, genitals, thighs, and lower abdomen was severely inflamed and numerous vesicles and blebs were scattered over this area. The infant appeared perfectly well otherwise. The mother stated that the diaper removed that morning had a very strong odor, "just like ammonia." She had saved the diaper in a closed receptable. On unfolding the wet diaper, a very strong penetrating odor of ammonia was noticed. So strong was this gas that it irritated my eyes very disagreeably during the examination. It seemed clear to me that the skin lesions were induced by the ammonia in the urine, since ammonia is a powerful rubofacient and vesicant.

"This case served to interest me in the study of ammonia in the urine and the resulting lesions, and for many years facts in regard to this condition were collected and form the basis for this study.

"The ammoniacal diaper is frequently encountered by the practitioner. Usually, the odor of ammonia is faint, especially in young infants. Only occasionally does the concentration become sufficiently intense to produce the characteristic irritation of the skin. The severest grade occurs in infants between one and two years of age.

"The lesions consist of inflamed areas on the inner side of the thighs, the genitals, the buttocks and lower abdomen. Sometimes the whole diaper region shows a diffuse redness.

"More characteristic is the appearance of vesicles or blebs. There may be only one at the end of the prepuce; often this is associated with others on the prominent parts of the genital region. It is the parts which come in direct contact with the diaper which show the blisters. Rarely the whole diaper region may show numerous confluent blisters. No vesication may be observed, but after the intense congestion, sometimes the whole epidermis becomes hard, cracked, and the skin seems covered with thin parchment. The dead skin separates in a flaky desquamation.

"A very important lesion, to which no attention has been given by pediatrists, is the formation of a blister at the meatus. This occurs only in boys who have been circumcised. The prepuce protects the meatus in the uncircumcised. The blister ruptures and a superficial ulceration remains. This causes distress in urinating and may be the source of hemorrhage. The ulcer is exceedingly troublesome at times. It becomes covered by a thin crust, which may partially or entirely occlude the orifice of the urethra, so that urination is painful and difficult. The passage of the the urine removes the crust and the ulcer is irritated again by the urine. Healing, therefore, may take several weeks. A troublesome stricture sometimes follows.

"The skin lesions nearly always appear in the morning when the infant has lain for a long period during the night. Infants who do not wet the diaper are not subject to this trouble. In fact, enuresis and ammoniuria go together. The assumption that the enuresis depended on the ammonia in the urine was entertained for awhile; the reverse is probably true.

"The ammoniacal diaper is a frequent precursor of pyelocystitis in female infants. The irritated genital region becomes more susceptible to infections. On account of the protection afforded by the labia, the urethral orifice in the female is not subject to the blistering.

"The association of the ammoniacal diaper and the exudative diathesis is frequent. The irritating urine initiates patches of eczema in the diaper region, which are exceedingly intractable unless the urinary condition is relieved.

"The onset is usually abrupt and the course is very irregular and indefinite. The irritating urine may be present for one day only; then, it may last for weeks.

"For several years I studied this condition clinically, after having read the article by Southworth. The original description by the French author, Jacquet in 1886 (the diaper rash is often called Jacquet's disease) was overlooked.

"While we pass over the cases in which a slight ammoniacal odor of the bedding is noticed, in the last five years I have collected brief notes of seventy-eight cases, in all of which the patients showed some skin lesions, and the ammonia was sufficiently intense to warrant more than a passing notice.

"Of these seventy-eight cases, fifty-four, or about three-fourths, occurred in children over 10 months of age. The worst cases are observed, not in infants, but in young children, from 1 to 4 years of age. By far the greater number of cases occur in the winter months.

"The severest lesions in my series have occurred in boys. As already mentioned, pyelocystitis, not infrequently follows the occurrence of a severe ammoniacal condition in girls. It seems to me this predisposing cause to pyuria should be given more attention.

"While several infants were fed partially on the breast, the disorder seems to be almost limited to artificially-fed infants. The severest grades arise at the time when the infant is beginning to to take solid food. Mixtures containing cow's milk and cereal decoctions are especially prone to result in the ammoniacal diaper. Taking large quantities of bread was etiologically related in a few cases. Egg also seemed to be a disturbing factor.

"The influence of diet was studied in many cases. In three infants the mothers insisted that the ammoniacal odor was stronger when orange juice was given. Acids and alkalies, in moderate doses, had no effect.

"We analyzed so many specimens of urine and corroborated Keller's original statement that a diarrheal disease induces an ammoniura, that there is an increase of ammonia to take the place of alkalies. Curiously, we did not prove that an acidosis existed when the free ammonia was detected in the diaper. Still, as most of the cases occurred in children one or two years of age, I favored the theory of acidosis. Our tests seemed to corroborate this hypothesis. Our figures seem to be conflicting and no positive conclusions could be drawn.

"Since an increased ammonia nitrogen was found in most of my

cases, we made an actual test. A new diaper was saturated with the suspected urine after it had been washed in soapy water and the excess of water squeezed out; the urine was poured into this diaper. The diaper was folded and kept in a warm place. Plenty of free ammonia arose from the cloth in a few minutes. The conclusion was that a washing soap strong in alkalies, not sufficiently rinsed, was the chief chemical that produced free ammonia. Nevertheless, bacteria may decompose some of the end-products and also generate this gas, as is clearly manifested in the diaper of the baby—or even that of the adult. But the chief source is supposed to be urea, which Cooke's studies emphasized (Am. J. Dis. Child., 1921). However, Van Slyke has shown that none of the urinary ammonia is derived from urea, but can not ammonia be produced from urea after it is excreted?

"Such a common disorder and we are still debating the course!

"After the publication of Cooke's article the custom of soaking the diaper in a weak solution of corrosive sublimate came to be the fashion, but the practitioner positively refused to follow the directions for the possibility of chronic mercury poisoning could not be excluded. Then other less toxic diaper antiseptics were proposed (Diaperine), and prescribed.

"But the old theory of relative acidosis emerged again. The excretion of ammonia and its salts was a metabolic disturbance and could be almost completely prevented dietetically by increasing the methionine.

"To 54 infants with ammoniacal urine, three grains of metione (granulated methionine) was prescribed daily for a period of one to four weeks. The urinary ammonia disappeared in two or three days."

We come back to my original statement: free ammonia seems to be caused by two etiological factors: (1) bacterial decomposition, (2) metabolic disturbance. Allergy in this group should also be considered.

The practitioner will order the diet changed—less milk, more meats, bread and vegetables.

Wash the diapers and pads thoroughly, get rid of all the soap and boil the diapers and pads.

Studies are needed to clear up this subject.

SIMPLICITY AND ECONOMY

JOHN ZAHORSKY, M.D.
St. Louis.

In two or three articles emphasis has been placed on simplicity and economy in pediatric practice. Physicians have the unfortunate habit of trying to improve the practice without considering the cost. In 1895 to 1900—a period of depression—I waited on many patients of the poor, who had little work at low wages. It, therefore, strengthened my outlook acquired during my childhood, that economy should be an essential professional consideration.

In the first place the home must be considered the unit of our democracy, and it is inconceivable at present that any other unit will replace this under some fantastic order of socialism. The individual family, living in one sheltered place, apart from others, mingling with other families only part of the time, yields not only the most natural and happy mode of life, but what is most important to physicians, also offers the most effective means of isolation in the prophylaxis of communicable diseases. Monogamy, carried out in its strict religious sense, is the most important prophylactic measure against syphilis and gonorrhea. The true and happy family life is the most important safeguard against a host of contagious diseases which will readily occur to any physician. The young child, who is happy in its home and remains constantly under the care of its parent, is saved from many diseases. The trouble begins when another child of the family is compelled to mingle with others at school, church or other public places and brings disease to the home.

If the home is the best isolating place against disease it also is the natural place for the sick child to be treated. When the young child is sick it is happiest and shows the strongest resistance when under parental care in its home. The practice of tearing the sick child from its mother's arms and taking it to a hospital, under strange surroundings, looked at by strange faces, administered to by strange methods, and deprived of loving caresses by the parent is not good pediatrics, whether the disease is influenza or poliomyelitis. In fact, the children's hospitals of the country have as yet not proven their value, except for the scientific study of disease and for those unfortunate little ones who have no home.

I declare, therefore, that successful pediatrics must maintain and develop the principles and practice of home prophylaxis and therapeutics, and not be carried away by the costly idealism of children's hospitals, asylums and clinics. These are only side units to the main show, and valuable to make up certain deficiencies of the home, but they can never take the place of the principal performance.

Fully 95 per cent of my own practice is in the home and private office. Hospital care is reserved for operative cases, chronic cases which come from out of the city, and a few requiring a most intensive observation and study for diagnosis.

It is a fact that the majority of pediatricians treat their children in the home in spite of the fact that the hospitals in the large cities are everywhere available. So some of us insist that a pediatrician is really a practitioner in the home and office. Hospital care is required in less than five per cent of all cases.

There is one thing that is demanded of the pediatrician. His work must be efficient. Great efficiency can only come after much practice, which is constantly improved by the correction of mistakes. The best work of physicians is generally done when watched by an anxious parent. This stimulus to do one's best rarely develops in hospital work where so much detail and labor is left to subordinates and nurses. Efficiency means careful work and hard thinking. It does not mean laboratory tests and consultations except after mature thought. The vast majority of diseases in children are readily diagnosticated on hearing the history of the case, and examining the patient once or twice. But the physician must have the habit of always examining the patient, and he must know what to look for, hence special training is essential; I would say not only special training in a hospital but training by a pediatrist in the home. The most successful pediatricians are those who act for a time as assistants to other practitioners.

To training in efficiency we need to add training in economy. At every step in a pediatric practice the question of cost must always be considered. The people who have children are young people, most of them just commencing life's work. They may have wealthy parents but the young people prefer to pay their own way and achieve their own success. The expense mounts up with the appearance of every child and every illness increases the cost. That

pediatrician is negligent of his duty when he does not consider cost in all his work. He must acquire a frugal method of thinking which is soon recognized by the family. Not for a moment would I tolerate the insinuation that pediatric practice should be cheapened. Whenever necessary to save the child's life or prevent another illness the pocketbook must be mercilessly squeezed. At the same time expense must be spared whenver it is safe and right to do so by the avoidance of expensive tests when simple tests are just as efficient; by prescribing the cheaper drugs when they are as efficacious as an expensive medicament; by the use of home nursing force instead of trained nurses, etc.

Even the physician must be honest in his charges. No other branch of medicine must so rigidly hold to that great rule of medicine as enunciated in the "Principles of Medical Ethics."

Should we not instruct mothers and even train them for efficient nursing, especially if they have not had any instructions from the hospital nurses? These days there is an abundance of textbooks available. The Children's Bureau of Washington will send a guiding booklet on child care for the asking.

The physician who does good work in an impersonal clinic or hospital will do still better work in the home of the patient where his personality is scrutinized and his efficiency is measured. (J. Missouri S. M. A., March, 1922.)

TREATMENT OF PERNICIOUS ANAEMIA WITH VERY SMALL QUANTITIES OF PYLORIC MUCOSA AND VITAMIN B_{12}. (Brit. M.J., 50:838-841, April 10, 1954). Dried pyloric mucosa from pig's stomach given alone exerts a definite antianemic effect, even in very small doses, but this effect is slight. However, these same doses given in combination with vitamin B_{12} in quantities that in themselves are ineffective when given orally exert a strong antianemic effect. The author obtained excellent results with a commercial preparation, Cycloplex MCO, in daily dosage of 0.15 gm. of dried pyloric mucosa and 15 mcg. of vitamin B_{12}. To be on the safe side in the routine treatment of pernicious anemia patients, a dosage is recommended corresponding to 0.3 gm. of dried pyloric mucosa and 30 mcg. of vitamin B_{12} for the initial doses. The maintenance dose has yet to be fixed.—*J.A.M.A.*

DEPARTMENT OF ABSTRACTS

SIEGEL, M. AND GREENBERG, M.: RISK OF PARALYTIC AND NONPARALYTIC FORMS OF POLIOMYELITIS TO HOUSEHOLD CONTACTS. (Journal American Medical Association, 155:429, May 29, 1954).

This study on multiple cases of poliomyelitis in households in New York City reveals two relationships between the initial type of disease in the household and the outcome among household contacts. First, the probability that more than one case will develop in a family is greater when the initial case is paralytic than when it is nonparalytic and the age span of susceptibility is increased. Second, the prognosis of the subsequent cases that develop in the affected households is worse both for life and for paralysis if the initial case is paralytic. The explanation of these results is speculative. The practical considerations seem fairly clear. First, the clinical type of disease that is first seen in a household is of some prognostic significance with respect to the occurrence of other cases, their clinical types, and case fatality. Second, the need for protection of contacts is greater if the initial case is paralytic than if it is nonparalytic.

AUTHORS' SUMMARY.

CLEMENTS, E. M. B.: CHANGES IN THE MEAN STATURE AND WEIGHT OF BRITISH CHILDREN OVER THE PAST SEVENTY YEARS. (British Medical Journal, 4842:897, Oct. 24, 1953).

Anthropometric measurements of children aged from 5 to 13 years, made between 1880 and 1947, have been standardized and examined. The average stature and weight have increased by from 2.5 to 3.5 inches and from 4 to 11 pounds, respectively, over this period, the increases being greatest in the older children. The increases found are greater than can be accounted for by systematic and random sampling errors, and indicate that, on the average, there has been an acceleration of 18 months' growth. Thus an average 6-year-old child is now of much the same size as one of 7.5 years in 1880. The rate of increase in mean stature and weight is not constant over the years. It begins slowly, and is first evident in the lower income group and in the 5 to 7 year old children in the upper and middle income groups. The rate of increase was

greatest in the inter-war years, when it was shown by all groups. The upward trend was interrupted during both the first and second world wars. The increase in the mean measurements has been greatest in the lower income groups, so that the difference which existed in 1880 between the average measurements of children in this group and the middle income group no longer exists. The differences in stature and weight between average children in the upper and lower income groups were 4 inches and 7 pounds in the late 19th century and 2 inches and 2 pounds in 1947.

AUTHOR'S SUMMARY.

LORD, J. M.: FOETAL ASCITES. (Archives of Disease in Childhood, 28:398, Oct. 1953).

Foetal and neonatal ascites is usually ascribed in textbooks of pediatrics to congenital syphilis. This has in fact become a rare cause of the condition. Two cases are reported of ascites associated with obstructive lesions of the lower urinary tract. Both patients were male, one being 5 weeks old when the diagnosis was made, and the second newborn. The diagnosis was suspected in the second patient, but unfortunately he died of atelectasis before the ascites could be relieved. A study of the literature shows that ascites may occur in cases of cirrhosis, foetal peritonitis, agenesis of intra abdominal organs and imperforation of the anus. Congenital obstruction of the urethra is the most common cause of foetal and neonatal ascites. Two main types occur. In the first there is an associated malformation of the anus, and the urinary tract abnormality is gross and the prognosis poor. In the second, and apparently commoner type, there is an isolated urethral obstruction in the male, and prompt surgical treatment may be effective. Success in one such case has been reported. Once suspected, the diagnosis is easy to establish, and it is important that this cause of foetal ascites should be recognized. AUTHOR'S SUMMARY

SIDBURY, J. B. AND SIDBURY, J. B., JR.: INFANTILE CORTICAL HYPEROSTOSIS. AN INQUIRY INTO THE ETIOLOGY AND PATHOGENESIS. (New England Journal of Medicine, 250:309, Feb. 25, 1954).

Infantile cortical hyperostosis is thought to be the clinical manifestation of an inherited defect of the arterioles supplying the

affected areas. The resulting hypoxia causes focal necrosis of the over-lying soft tissues and proliferative reaction of the periosteum. A genetic factor is postulated because of the occurance of the condition in siblings and its association with other congenital anomalies. This condition is usually noted during the first 5 months of life and is characterized by a triad of fever, irritability and swelling over bone. These symptoms might appear in any order. The prognosis and course is usually considered to be benign. However, there are 4 recorded deaths, 3 due to infection and the other of unknown cause. Hormonal therapy (ACTH and cortisone) has been tried in 12 cases and appears to have shortened the course of the illness. MICHAEL A. BRESCIA, M.D.

RENDLE-SHORT, J. AND HAVARD, C.: INCARCERATED AND STRANGULATED INGUINAL HERNIA IN THE FIRST YEAR OF LIFE. REPORT ON 45 CASES. (British Medical Journal, 4863:680, March 20, 1954).

Forty-five cases of incarcerated inguinal hernia under 1 year of age have been studied; of these, 44 were in boys, and 42 were on the right side. The cases have been divided into 2 groups: Group 1, presenting with symptoms of intestinal obstruction, comprised mainly the younger babies, in whom often no hernia had been noticed before. There were 29 babies in this group and 18 per cent of these died. Group 2 consisted mainly of older babies in whom an easily reducible hernia had been observed previously, but in whom the hernia had suddenly became irreducible; obstructive symptoms were minimal. There were 16 babies in this group and no deaths. It has been shown that, in the age group 1 week to 3 months, strangulated inguinal hernia is the commonest, almost the only, cause of intestinal obstruction. Owing to the ease with which an inguinal hernia can be missed in a baby, it is essential that the inguinal region should be carefully examined in every infant presenting symptoms of acute intestinal obstruction.
AUTHORS' SUMMARY.

GORDON, H. H.; LUBCHENCO, L. AND HIX, I.: OBSERVATIONS ON THE ETIOLOGY OF RETROLENTAL FIBROPLASIA. (Bulletin Johns Hopkins Hospital, 94:34, Jan. 1954).

The incidence of residual lesions of retrolental fibroplasia in

211 prematurely born infants, weighing less than 1.5 kg. at birth, was analyzed in relation to oxygen administration. Restriction of oxygen led to a marked drop in incidence over a 2 year period in both residual lesions and membranes as compared with a previous period of unscrutinized high oxygen therapy. Survival rates were not adversely affected by restriction of oxygen. A discussion is given of factors other than high oxygen which may contribute to the etiology of the disease. AUTHORS' SUMMARY.

ANDERSON, G. W. AND RONDEAU, J. L.: ABSENCE OF TONSILS AS A FACTOR IN THE DEVELOPMENT OF BULBAR POLIOMYELITIS. (Journal American Medical Association, 155:1123, July 24, 1954).

It has been found that persons with the bulbar type of poliomyelitis give a history of removal of the tonsils more frequently than do persons with other forms of poliomyelitis and that, if clinically recognizable poliomyelitis develops in a person who has had his tonsils removed, the likelihood of bulbar involvement is four times as great. This higher proportion occurs at all ages regardless of the time that has elapsed since operation. It is possible that the excess of bulbar involvement in persons who have had tonsillectomy is due to direct invasion along fibers of the 9th and 10th cranial nerves. No evidence was found as to the effect of tonsillectomy in altering susceptibility to clinically recognizable poliomyelitis. MICHAEL A. BRESCIA, M.D.

ALLEN, F. H., JR. AND DIAMOND, L. K.: PREVENTION OF KERNICTERUS. MANAGEMENT OF ERYTHROBLASTOSIS FETALIS ACCORDING TO CURRENT KNOWLEDGE. (Journal American Medical Association, 155:1209, July 31, 1954).

A large experience with erythroblastosis fetalis makes several points clear. 1. Kernicterus is the only important cause of death and crippling after the first day of life. 2. Kernicterus is preventable by exchange transfusion that may be repeated if necessary to keep the bilirubin level from rising above 20 mg. per 100 ml. 3. Blood factors other than the Rh are important cause of erythroblastosis fetalis and kernicterus. These must be recognized, especially in the babies of Rh positive women, and prompt treatment must be given when indicated. 4. No prenatal treatment, to date, in-

cluding the administration of steroid hormones, has been proved effective. AUTHORS' SUMMARY.

FOLEY, J. C.; DREYER, N. B.; SOULE, A. B., JR. AND WOLL, E.: KEROSENE POISONING IN YOUNG CHILDREN. (Radiology, 62:817, June 1954).

Kerosene poisoning is a relatively common accident occurring in children between the ages of 8 months and 2 years, especially in areas where kerosene is used for cooking and other household purposes. The major effect, apparently produced by aspiration either of kerosene itself or of gastric contents during vomiting or gastric lavage, consists of a rapidly developing bronchopneumonia with "asphyxial membranes" which, when sufficiently marked, may lead to respiratory failure and death. Depression of the higher cerebral centers may occur from absorption of toxic fractions of kerosene or of impurities within it, probably from the stomach and intestinal tract. If pneumonia develops, it is usually bilateral and may be widely disseminated; it reaches its peak within 2 to 8 hours following exposure, with gradual regression after this time. Due to the highly toxic effects of even small quantities of kerosene introduced intratracheally, it seems apparent that in most cases gastric lavage should not be done at all or, if done, should be performed only after introduction of an intratracheal tube with balloon inflated. The public should be educated regarding the grave dangers to young children from drinking or aspirating kerosene.
AUTHORS' SUMMARY.

SPAIN, D. M.; BRADESS, V. A. AND GREENBLATT, I. J.: POSSIBLE FACTOR IN SUDDEN AND UNEXPECTED DEATH DURING INFANCY. (Journal American Medical Association, 156:246, Sept. 18, 1954).

In three infants who died suddenly and unexpectedly, postmortem serum gamma globulin determinations were made and found to be exceptionally low. Postmortem determinations in two control infants of the same age group showed normal gamma globulin levels. It is suggested that a lowered antibody level or gamma globulin level or both may be an important factor in many of these sudden and unexpected deaths occurring during infancy.
AUTHORS' SUMMARY.

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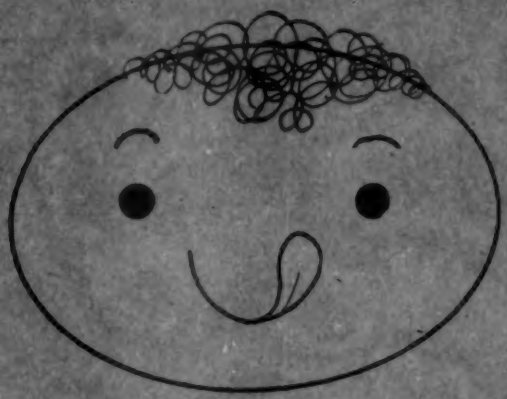

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*Lawler, E. G. et al.: Clin. Med. 61:207 (March) 1954.

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